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REMARKS/ARGUMENTS

Further responsive to the Office Action of May 7, 2007 and responsive to the telephone conferences with the Examiner of June 14, 2007 and July 7, 2007.

The claims under examination are 124 to 126, 129 to 131, 140 to 144, 146 and 147.

Claims 127, 128,132 to 136 and 145 are withdrawn from further consideration as non-elected.

Claim 124 has been amended to specify that the method involves a plurality of body fluid samples from different subjects. This language simply puts into words the significance of the discovery of the detection of seroconversion associated with NANBV infection at early times after infection through the use of the capsid antigen. Such time of detection following infection would have been understood by those skilled in the art when applied across a plurality of samples from different human subjects since obviously specifying that an antigen is an early marker, i.e. capable of detecting antibodies appearing after early infection, is not meaningful on an individual patient basis. The characteristic of an early marker is that in a plurality of samples said marker is detecting the presence of antibodies to an infectious agent earlier than other markers are able to detect the presence of antibodies to the infectious agent. Due to inevitable

differences in the immune response afforded by individual patients such an assertion cannot be made with a single patient in a meaningful way, since a firm conclusion regarding the marker's ability to detect an antibody early or late would, in such an instance, not be statistically valid.

Such early detection is, of course, highly significant when applied to many samples such as in a blood bank. No single antigen is ever 100% effective in detection. The combination of the capsid and C-100-3 antigens in claim 141 is uniquely effective in reducing the risk of non-detection in both individual cases and across multiple samples from different subjects.

Paragraphs 1 to 8 of the Office Action do not call for responses.

Paragraph 9 states that the title is missing from the first page of the Specification. The Amendment to the Specification filed on September 7, 2006 includes the title. The Substitute Specification containing the title was also filed on September 7, 2006. We confirm that submission of the title in the September 7, 2006 Amendment and Substitute Specification was reached to the satisfaction of Examiner Lucas during a telephone call on May 22, 2007.

Paragraph 10 does not call for response.

In response to paragraph 11, the Specification does not contain new matter. As stated in the Declaration of Joseph E. Mueth filed February 13, 2006, all of the material added by amendment is found in United States Patent Application Serial No. 07/573,643, filed August 27, 1990 and United States Patent Application Serial No. 07/616,369 filed November 21, 1990. The disclosures of these two patent applications were incorporated by reference in the instant patent application as filed with the Preliminary Amendment on October 1, 2003. See also the Declaration of Joseph E. Mueth filed February 13, 2006, Exhibit 1 thereto which is the Patent and Trademark Office file history containing United States Patent Application Serial No. 07/616,369 filed November 21, 1990. Exhibit No. 2 to the Joseph E. Mueth Declaration of February 13, 2006 contains the file history of United States Patent Application Serial No. 07/573,643, filed August 27, 1990.

At the request of the United States Patent and Trademark Office, a Substitute Specification to textually incorporate all prior amendments to the Specification was filed on September 7, 2006. Please note that the Substitute Specification was filed as part of an amendment and as a separate, attached document. This introduced a difference in pagination. In the following citations to the Substitute Specification, we refer to the attached Substitute Specification and not to the Specification as it appears in the text of the Amendment filed September 7, 2006. Pages 126 to 130 to the "Remarks" forming part of the Amendment of September 7,2006, contains a road map showing the genesis of every amendment to the Specification, filed subsequent to the October 1, 2003 filing

date of the instant patent application. There is no new matter.

Paragraphs 12 to 14 do not call for response.

In paragraph 15, claims 112 to 114 were previously rejected under 35 U.S.C. 112, second paragraph, as being indefinite. As the Examiner is aware, claims 112 to 114 were replaced by claims 124 to 126. Presumably, the Examiner's comments in paragraph 15 of the Office Action would apply to claims 124 to 126. Applicant has now revised claims 124 to 125 and the method has been further defined as one using a plurality of body fluid samples from different subjects which are each tested by a method for detecting early seroconversion associated with NANBV infection at early times after infection, the method thereby reducing the number of false negatives reported across the plurality of samples from different human subjects. This rejection should be withdrawn. Since early treatment or other measures are generally known to work more efficiently in ameliorating the sequelae following an infection with a pathogen (such as a Non-A, Non B hepatitis agent), it is clearly of interest to strive to achieve the detection of antibodies as early as possible following occurrence of the infectious event -- in fact, for any disease. As for Non-A, Non B hepatitis, this aspect is particularly important within the context of blood donors, as any undetected infectious agent present in the donated blood is likely to lead to the transmission of the infectious agent to the recipient of the donated blood and thereby transfer the disease.

The Specification clearly states the shortcoming of the state-of-the-art test of 1990, which used the C-100 antigen of HCV. See page 4, second paragraph, to the top of page 5 of the Substitute Specification as filed on September 7, 2006:

> However, the C-100-3 antigen based immunoassay has been reported to preferentially detect antibodies in sera from chronically infected patients. C-100-3 seroconversion generally occurs from four to six months after the onset of hepatitis, and in some cases C-100-3 fails to detect any antibody where an NANBV infection is present. Alter et al,, New Engl. J. Med., 321:1538-39 (1989); Alter et al., New Eng. J. Med. 321:1494-1500 (1989); and Weiner et al. Lancet 335:1-3 (1990). McFarlane et al. Lancet 335:754-757 (1990), describe false positive results when the C-100-3-based immunoassay was used to measure antibodies in patients with autoimmune chronic hepatitis. In addition, Gray et al., Lancet 335:609-610 (1990) describe false positive results using C-100-3 -based immunoassay on sera from patients with liver disease caused by a variety of conditions other than HCV....**A NANBV immunoassay that could accurately detect seroconversion at early times after infection, or that could identify an acute NANBV infection, is not presently available.** [emphasis added]

The rejection should be withdrawn.

Paragraph 16 does not call for a response.

In paragraph 17, claims 124 to 126, 129 to 131, 137 to 144, 146 and 147 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

The newly submitted claims address this point by making it clear that in the method of the invention, the antigen can be affixed to a solid support or matrix or not. The claims do not further specify since the method is generic in this regard. It was well known to carry out antigen-antibody reactions in various ways. In any event, see the Substitute Specification, filed September 7, 2006, pages 36 to 38, which refers to the ELISA format using, for example, the antigen bound to a solid phase. The antigen can also be provided in solution as a dispersion, page 37, last paragraph. This is consistent with and supported by the Specification at page 39, cited by the Examiner (apparently intended to refer to the Substitute Specification at pages 36 to 38).

The Office Action states "This language implies that the antigen is in soluble form in the implicit aqueous medium" This is not correct. In the present method, the admixture can be a mixture of elements present in the same, or, different physical phases, (the three commonly known phases are, gas, liquid, or solid state). With

regard to a disclosure of an antigen which is not affixed, see also the Substitute Specification filed September 7, 2006 at pages 64 et. seq. On page 68 of the Specification, third full paragraph, reads, "The reagent is typically affixed to the solid matrix by adsorption from an aqueous medium although other modes of affixation, well known to those skilled in the art can be used". Further, on page 73 of the Specification, middle paragraph, the application of a format for competitive immunoassays requiring both soluble and solid phase antigens of the Invention is disclosed. See pages 76, middle paragraph, third sentence, "The method comprises admixing a body fluid sample (1) with a solid support having affixed thereto an antibody according to this invention and (2) a labeled NANBV structural protein of this invention to form a competition admixture that has both liquid and a solid phase". See also page 69, first full paragraph, " The NANBV structural protein, fusion protein, labeled specific binding agent or amplifying reagent of any diagnostic system described herein can be provided in solution, as a liquid dispersion or as a substantially dry powder, e.g. in lyophilized form." See also page 70, first full paragraph, "Various heterogeneous and homogenous protocols, either competitive or noncompetitive, can be employed in performing an assay method of this invention. Thus, while exemplary methods are described herein, the invention is not so limited."

This rejection should be withdrawn.

In paragraph 18, claim 131 was rejected under 35 U.S.C. 112, second paragraph as being indefinite. The Examiner queries whether the claim in regard to CAP-B requires only residues 21 to 40 of the capsid or more. It appears that claim 131 is perfectly clear: SEQ ID NO: 73 shows the entire capsid region; claim 131 states that said capsid antigen is selected from a group which consists of several discrete subsections of the capsid. CAP-B is one of them.

Turning to the Examiner's query regarding the definition of CAP-N antigen, see the footnote on page 101 of the Substitute Specification which identifies the CAP-N antigen as the N-terminal of the putative capsid protein. This is the aa 1-74 of SEQ ID NO: 73, see also page 105 which precisely refers to the "fusion protein containing CAP-N antigen and produced by the vector pGEX-3X-690:694". The preparation of this vector is described beginning on page 84 of the Specification, "B. Production of Recombinant DNA (rDNA) that encodes a Fusion protein" and is summarized on page 86, middle paragraph, which reads:

> The nucleotide and predicted amino acid sequence of the pGEX 3X-690:694 fusion transcript from the GST sequence through the 690:694 insert is presented in SEQ ID NO: 73 and SEQ ID NO: 74, respectively. The resulting rDNA molecule, pGEX-3X-690:694, is predicted to encode a NANB fusion protein having the amino acid residue sequence shown in SEQ ID NO: 74 from the amino acid residue 1 to residue 315. The

resulting product generated from expression of the plasmid is referred to as the NANBV capsid protein amino terminus (CAP-N)

See also Mueth Declaration on file, Exhibit 2, Specification of United States Patent Application Serial No. 07/573,643, page 57, lines 21 to 30.

This rejection should be withdrawn.

Paragraph 19 requires no response.

In paragraph 20, claims 124 to 126 and 129 to 131 are rejected on Houghton, United States Patent No. 5,350,671 under 35 U.S.C. 102(e). Houghton ('671 patent) does not teach detecting seroconversion at early times after infection. Houghton contains only a single reference to the immunologic reactivity of structural antigens, which reads as follows, United States Patent No. 5,350,671, column 83, lines 16 to 32:

> As seen from the results shown in Figure 65, a number of clones expressed polypeptides containing HCV epitopes which were immunologically reactive with serum from individuals with NANBH. Five of these polypeptides were very immunogenic in that antibodies to HCV epitopes in these polypeptides were detected in many different patient sera. The clones encoding these polypeptides and the location of the

polypeptide in the putative HCV polyprotein (wherein the amino acid numbers begin with the putative initiator codon) are the following: Clone 5-1-1 amino acids 1694-1735, clone C100 amino acids 1569-1931; clone 33c amino acids 1192-1457; clone CA279a, amino acids 1-84; and clone CA290a amino acids 9-177. The location of the immunogenic polypeptides within the putative HCV polyprotein are shown immediately below.

The Table in Figure 65 of Houghton lists what appears to be a series of samples of a "Chronic HCV Patient C100 positive" which shows that the two core antigens, identified as CA 279a and CA 290a, which Houghton discloses, actually only score as reactive with samples no. 5-8, not the first four samples of the C100 positive panel. In contrast clones C33c as well as clone 5-1-1 (the latter constituting a part of the C100 antigen, see Houghton, Figure 69) both score as reactive with all these eight specimens. Similarly, in the leftmost columns of Figure 65, Houghton presents three serum specimens as "1. Post acute", "2. Post acute" and "3. C100 Conversion" respectively. None of these score as reactive with his capsid antigens

Hence, even with regard to actual data presented, Houghton teaches away from the subject matter of the present invention. There is no motivation in Houghton to investigate the possibility that the HCV antigens related to the capsid region CA279a and CA 290a, that sera obtained at early times after infection might score as reactive

when using a capsid antigen.

It is therefore noted that Houghton fails to distinctly identify and point out the problem associated with serology based on the C-100-3 antigen in that the later antigen is not associated with detection at early times after infection the presence of antibodies to HCV (see references supra). The lack of acknowledgment of the problem inevitably leads to a failure to provide the solution to this problem, namely the provision of a method for detection at early times after infection (which method incorporates providing a capsid antigen encoded by HCV structural gene sequences as disclosed in the present application). In fact, Houghton teaches away from the solution by merely disclosing that several antigens, including both the C-100-3 and structural antigens were "very immunogenic" (see the citation from above), thus failing to discriminate between or recognize their distinct properties. In contrast, the instant application clearly presents the problem, and its solution.

The term seroconversion, is understood as the development of specific antibodies to microorganisms in the serum as a result of infection. Serology (i.e., the testing for antibodies, typically using blood serum -- hence the term "serology" -- but also, in a broader sense, from other sources, such as saliva, urine, etc.) is used to determine antibody positivity. Prior to seroconversion, a specimen of blood will test as seronegative for the antibody for which a particular test antigen is applied. After seroconversion, the blood will test as seropositive for the antibody with regard to the

same test antigen. It follows that the time point at which seroconversion occurs may be dependent on which particular antibody specificity is being tested for (i.e. which test antigen is being applied). Initially, available test designs for determining seronegativity or seropositivity for HCV were limited to using the C-100-3 antigen as test antigen. Hence, seroconversion was defined in relation to the C-100-3 antigen, which enabled clinical investigators to conclude that patients infected with HCV tended to seroconvert at late times after infection, i.e. during the chronic phase of the disease. A person skilled in the art would be familiar with such situations, irrespective of the particular infectious disease under study, see Ameisen, JC et al., AIDS Res, Hum. Retroviruse, (1989) Jun:5(3)279-91; Boucher, CA et al., AIDS 1989 Feb:3:(2):7; Mushahwar, IK et al., Am. J. Clin. Pathol., (1981) Nov:76(5):692-7; Shattok, AG et al., J. Virol. Methods, (1989) Mar:23(3)233-401; Stramer, SL et al., JAMA, (1989) Jul:7:262(1):64-9; Bahraoui, E et al., Blood, (1990) Jul1(1):76:527-264. Whether or not in the context of the present invention, a different antigen (i.e., still derived from HCV but different from the C-100-3 antigen) might be useful to determine the presence of antibodies directed against the HCV at an earlier time following the time point of infection, was unknown, albeit a possibility. If, for instance, antibodies to the C-100-3 antigen indeed were formed and, consequently, detected at a time later than the appearance of antibodies recognizing other HCV related antigens, the seroconversion related to the latter antigen would be stated to occur earlier than that established for the C-100-3 antigen. Which antigen, if any, might be preferred in this regard was unknown until experimental evidence was provided to substantiate its utility. Absent such evidence, the outcome is

not known and purely speculative. As an illustrative example see, e.g. Bahraoui, E., et al., Blood (1990) July 1(1) 76: 257-264, supra, a publication dealing with the potential use of the *nef*- antigen as an "early marker" for detecting HIV infection. As it turned out, this particular antigen did not provide the requisite characteristics to provide early detection of infection since the time of seroconversion was not significantly different from the time of seroconversion using several other antigens derived from the virus, however, the language as used clearly indicates that the readers of said publication will understand the terminology as employed by the authors. While the *nef*- antigen of HIV, contrary to initial belief, was unhelpful to demonstrate, earlier than heretofore, seroconversion with regard to HIV, the present application, in respect of HCV, did show, and continues to show, that a method for detection of seroconversion at early times after infection is indeed provided as disclosed in the present invention. This is also amply illustrated by subsequent publications on the subject matter and ELISA assays for detection of anti-HCV antibodies all now contain means to detect anti-capsid antibodies.

In summary, therefore, the literature, is now replete with references to the utility of the HCV capsid antigen as the antigen of choice for detection of anti-HCV antibodies at early times after infection. Obviously, no such publications can be cited which existed prior to submission of the present invention, however, the terminology exemplified by the use of words such as "early seroconversion", "Window between infection and antibody appearance", "early marker" and the like are plentiful (see

references cited supra).

In contrast, by Houghton United States Patent No. 5,350,671 there is no discrimination between the five antigens provided as they are merely stated to be "very immunogenic", all similar. The present invention demonstrates they are not similar.

Paragraph 24 rejects claims 124 to 126, 129 to 131, 138, 141, 144, 146 and 147 as being obvious from Houghton under 35 U.S.C. 103(a). The Examiner acknowledges that Houghton does not teach the combined use of capsid with C-100-3 antigen. Further, as discussed above, Houghton never had any early sera which were tested with capsid and did not teach that the capsid was uniquely effective in detecting early seroconversion and did not teach any way of minimizing the failure to detect early HCV infection. This problem was solved by the present invention.

Detection of NANBV infection with the use of the C-100-3 antigen is much later than if determined by the use of the capsid antigen according to the method of the present invention. To suggest that Houghton anticipated this is astonishing. Houghton does not disclose that any of the proteins described would be capable of detecting, earlier than any other, the presence of anti-HCV antibodies.

With particular reference to claim 141 to the combined capsid and C-100-3 antigens, the capsid detects early seroconversion as is explained above. The C-100-3 antigen detects what might be called later detection. The individual patient does not present as "early" or "late" infected. Thus, each antigen contributes to an overall major benefit in the detection of a wide range of HCV infections, both early and late. Houghton never disclosed that any HCV antigen was better than any other in this regard, and did not teach that this specific combination provided the best overall assay for the detection of HCV infection.

It is notable that in late or acute NANBV infection, the antibodies in a sample do not necessarily react with the capsid antigen, see Substitute Specification, page 104, Table 5, chimp 51 where there was no reaction with the capsid. These results as disclosed in the present patent application revealed for the first time the important benefit to be derived from using C-100-3 antigen ("Anti HCV" in Table 5) in conjunction with capsid antigen.

The rejections on Houghton should be withdrawn.

In paragraph 21, claims 124 to 126, 129 and 131 were rejected on Wang United States Patent No. 5,436,126 under 35 U.S.C. 102(e). The Examiner states that even though Wang is not prior art as that term is normally understood in light of the Declaration Under 37 CFR 1.131, (Office Action, paragraph 23), rejection on Wang is

nevertheless proper because the Wang patent and the instant patent application claim "the same invention". The newly submitted claims are clearly drawn to inventions which Wang did not claim (and could not have claimed). Wang did not claim detection of seroconversion at early times after infection using capsid antigen across a plurality of samples as stated in claims 124 to 126, 129 and 131. Wang is not "prior art" in any relevant respect. Wang does not teach the use of C-100-3 antigen with capsid antigen. The rejection on Wang should be withdrawn.

In paragraph 25, claims 124 to 126, 129 to 131, 138, 141, 143, 144, 146 and 147 were rejected on Wang United States Patent No. 5,436,126 in view of Houghton United States Patent No. 5,350,671 under 35 U.S.C. 103(a). Both of these patents are extensively discussed hereinabove and that discussion is incorporated by reference. Wang is not prior art as to the method using the capsid in the method of claim 124 in light of the Helting Declaration under Rule 31. Further, as the Examiner notes, neither Houghton nor Wang teach the use of the C-100-3 peptide with the capsid peptide for the detection of HCV antibodies. Consequently, the joint teachings of Wang and Houghton cannot be combined in any obvious manner to yield the subject matter of any of the claims.

Neither patent teaches the unique benefit of the combination of the two antigens to minimize the risk of failure to detect HCV infection.

The rejections on Wang or Wang in view of Houghton should be withdrawn.

The Examiner's comments in paragraph 26 regarding double patenting are noted. By the cancellation of claims 137 and 139, the issue of double patenting is eliminated. Claims 140 and 142 are free of double patenting.

Paragraphs 22 and 23 require no discussion.

All of the rejections should be withdrawn.

The Notice of Allowance is requested.

Date: July 6, 2007 Respectfully submitted,

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